

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:)
)
Thomas R. Cech et al.) Examiner: Unassigned
)
Serial No.: 08/912,951) Art Unit: 1815
)
Filed: August 14, 1997)
)
For: HUMAN TELOMERASE) STATEMENT REGARDING PRE-
CATALYTIC SUBUNIT:) EXAMINATION SEARCH
DIAGNOSTIC AND THERAPEUTIC)
METHODS)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants are submitting a Petition to Make Special under 37 C.F.R. 1.102(d), in the above-captioned application. Pursuant to M.P.E.P. § 708.02 VIII (c), Applicants hereby submit the following statement regarding the pre-examination searches that have been performed in connection with the above-captioned application.

1. A pre-examination search in connection with the presently claimed subject matter was performed at the request of the applicants by PRIOR ART SEARCHES, INC. (PAS), Arlington, Virginia, an independent firm. The search was supervised by Dr. D. J. Hansell (Ph.D. Oxon.), an employee of PAS. To conduct the search, applicants provided PAS with exemplary claims related to the subject matter claimed in the Present Application, a PTO Form-1449 prepared for USSN 08/724,643 (an application to which the above-captioned application claims priority), and copies of three scientific publications related to the invention (references EA, FK, and FL of the accompanying PTO Form-1449).

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According to PAS, their search was directed toward showings in prior art of telomerases. More specifically, the search was directed toward "the inventive combination of the characterization, DNA and amino acid sequences of the human catalytic protein subunit, referred to as telomerase reverse transcriptase (TRT)." The search was designed to include references published on or before August 14, 1997.

The searches carried out included:

An automated Patent System (APS) Computer full text search of U.S. patents and European and Japanese titles and abstracts;

A foreign Patent Access System (FPAS) Computer title search of foreign materials

The following databases were searched on STN for preparation, diagnostic and therapeutic applications of telomerase:

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|---------------------------|--------------|
| US Patents | 1972-present |
| World Patents Index | 1963-present |
| Patosep(European patents) | 1978-present |
| Patoswo(World patents) | 1983-present |
| Medline | 1966-present |
| Biosis | 1969-present |
| Scisearch | 1974-present |
| Embase | 1974-present |
| Chemical Abstracts | 1967-present |
| NLDB(Newsletter database) | 1988-present |

Search of NIH grant awards database

Manual PTO class search of U.S. patents in the following classifications:

Class 424 (Drug: Bio-Affecting and Body Treating Compositions)

Subclass 94.5 (enzyme containing transferases)

Subclass 146.1 (immunoglobulin, antiserum, antibody binding enzyme)

Class 435 (Chemistry: Molecular Biology and Microbiology)

Subclass 7.4 (measuring/testing assay to identify enzyme)
Subclass 15 (involving transferase)
Subclass 183 (enzyme; proenzyme; composition thereof; process for preparing)
Subclass 194 (transferring phosphorus containing group)
Class 536 (Organic Compounds)
Subclass 23.2 (DNA/RNA sequence encodes an enzyme)
Subclass 25.1 (3'-5' linked RNA)
Subclass 25.2 (2'-5' linked RNA)
Class 530 (Chemistry: Natural Resins or Derivatives: Peptides or Proteins)
Subclass 387.1 (immunoglobulin, antibody, or fragment thereof)
Subclass 388.26 (human monoclonal..binds enzyme).

Primary Examiner Robert Wax of Art Unit 1814 was consulted regarding the field of search. He confirmed that the subject matter of the invention belongs in many of the class/subclasses searched above.

The search also included the APS Computer full text search (1970 to date) for various "key words" and character fields. The following search statements (or combinations thereof) were conducted under the U.S. Patent file: telomerase?; ribonucleoprotein?; reverse transcriptase?; human. These key words were defined to appear anywhere in the text of the documents. The same search statement was conducted under the European and Japanese Abstract files. The information was downloaded and reviewed by subject title and abstracts so that any relevant selections could be made. The search additionally included the FPAS Computer title search for various "key words".

PAS reported to the Applicants that "We have considered hundreds of documents located in our search activity and we have not located showings of the subject human TRT." The results of the PAS search were reviewed by the undersigned and the references believed to

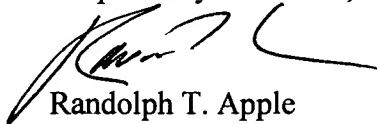
be most relevant or informative were selected for inclusion in the *Detailed Discussion of The Most Closely Related References* submitted herewith. A copy of the letter dated November 19, 1997, from PAS (with Attachments A, B and C) describing the search they carried out is attached as Appendix I.

2. A search was conducted by a foreign patent office for a related patent application. A patent application claiming priority to the above referenced application was filed in the United Kingdom (UK) on October 1, 1997. The UK Patent Office identified seven references considered to be relevant. The UK search report is attached as Appendix II.

3. Additional references related to the subject matter of the invention have been identified by the applicants based on their familiarity with the field.

Applicants have identified those references that the undersigned attorney believes are most closely related to the claimed subject matter. Applicants have also provided a detailed discussion of these references, which is submitted herewith, which discussion points out how the claimed subject matter is distinguishable over these references.

Respectfully submitted,



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Appendices:

1. Letter dated November 19, 1997, from PAS (with Attachments A, B and C).
2. Search Report of United Kingdom Patent Office

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| In re application of: |) | |
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| Thomas R. Cech, et al. |) | Examiner: Not Assigned |
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| Serial No.: 08/912,951 |) | Art Unit: 1815 |
| |) | |
| Filed: August 14, 1997 |) | |
| |) | |
| For: HUMAN TELOMERASE |) | <u>DETAILED DISCUSSION OF MOST</u> |
| CATALYTIC SUBUNIT: |) | <u>CLOSELY RELATED REFERENCES</u> |
| DIAGNOSTIC AND THERAPEUTIC |) | |
| METHODS |) | |

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants are submitting a Petition to Make Special under 37 C.F.R. § 1.102(d), in the above-captioned application (hereinafter, the "Present Application"). Pursuant to M.P.E.P. § 708.02 VIII(e), Applicants are submitting the following detailed discussion of the references which Applicants consider most closely related to the presently claimed subject matter. The discussion points out how the presently claimed subject matter is distinguishable over these references. Discussion of a reference should not be construed as an admission that the reference is prior art to the Present Application.

To identify references closely related to the presently claimed subject matter, Applicants relied on:

- (i) a pre-examination search carried out by Prior Art Searches, Inc. (Arlington, VA), as described in the *Statement Regarding Pre-Examination Search* submitted herewith;
- (ii) a search carried out by the United Kingdom (UK) Patent Office in an examination of a UK patent application claiming priority to the above-referenced

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application, and having claims directed to, *inter alia*, novel reagents and methods related to the catalytic protein subunit of human telomerase (*i.e.*, the same general subject matter under examination in the present case). A copy of the search report is attached to the *Statement Regarding Pre-Examination Search* submitted herewith;

(iii) other references known to the Applicants and/or Applicants' representatives.

Applicants note that the searches carried out by Prior Art Searches, Inc., and the UK Patent Office (i and ii *supra*) identified references in addition to those discussed *infra*. Those references listed in the searches, but not listed below, are either not believed to be highly relevant, are cumulative with other references discussed below, or both. For the Examiner's convenience, the two-letter identifier used in the accompanying PTO Form-1449 is given in brackets for each published reference discussed below. In addition to the published references discussed *infra*, Applicants also include brief descriptions of related U.S. and foreign patent applications to which the Present Application is related by a claim of priority or subject matter, noting the listed inventors and assignees for each application.

As an initial matter, Applicants point out that the claimed invention relates to, *inter alia*, isolated, purified, and recombinant preparations of the catalytic protein subunit of human telomerase, referred to as *human telomerase reverse transcriptase* or *hTERT*. The claimed invention also relates to, *inter alia*, isolated, purified, and recombinant variants and fragments of the full-length protein and nucleic acids encoding hTERT, as well as methods relating to the novel hTERT peptide, polypeptide, protein, oligonucleotide and polynucleotide reagents of the invention.

The following references are considered by Applicants to be most closely related to the claimed invention:

A. U.S. Patent No. 5,489,508 ("Therapy and Diagnosis of Conditions Related to Telomere Length and/or Telomerase Activity," issued in 1996 to West, et al.) [AM]

The '508 patent described the relationship between telomerase activity and telomere length and the ability of a cell to proliferate, and described a variety of diagnostic and

therapeutic methods relating thereto. The '508 patent also described a method of identifying telomerase inhibitors and activators that regulate telomere length or telomerase activity. The present methods and reagents relating to the catalytically active human telomerase subunit protein (hTERT) are not described in the '508 patent.

Continuation-in-part and divisional patent applications related to the '508 patent are pending or have issued as U.S. patent numbers 5,707,795; 5,686,245; 5,695,932; and 5,645,986. Because their disclosures, as they relate to the present matter, are believed to be cumulative with the '508 specification, they are not separately discussed.

B. U.S. Patent 5,583,016 ("Mammalian Telomerase," issued in 1996 to Villeponteau, et al.) [AL]

The '016 patent described compositions and methods relating to the RNA component of human telomerase, and the gene encoding it. Methods of using or targeting the telomerase RNA were also described, e.g., methods for detecting the presence or amount of telomerase RNA in a sample, and methods for treating a condition associated with telomerase activity using agents that target the telomerase RNA. The '016 patent described methods by which the telomerase protein subunit(s), or their genes, could be isolated, including affinity capture using the telomerase RNA or its complement as the affinity ligand and expression screening using labeled telomerase RNA as a probe. The '016 patent did not describe the present methods and reagents relating to the catalytically active telomerase subunit protein.

C. Japanese patent publication JP 09154575-A ("Telomerase useful in diagnosis of tumors - comprises RNA protein having aggregate containing protein located at terminal region of human chromosome," assigned to Soosei K.K (Abstract), published June 17, 1997[FF]

This publication described a putative human telomerase ribonucleoprotein, comprising three proteins (about 50, 80, and 140 kD), which is obtained from human tumor cells by homogenization, precipitation, chromatography and electrophoresis. The abstract appears to describe a relatively crude protein preparation, and does not provide any nucleotide or amino acid sequence.

D. WO 96/12811 ("Yeast Telomerase Components and Methods Using Them," Gottschling et al./Arch Dev Corp. published in 1996) [FA]

This publication described genes encoding template RNA of the yeast *Saccharomyces cerevisiae* and five "telomerase associated proteins" referred to as "STR1" and "STRs 3-6." The use of these agents to modify the proliferative capacity of a cell by modifying telomerase activity, for development of diagnostics and therapeutics, and for generation of anti-telomerase antibodies was described. Methods for isolating human genes encoding telomerase-associated proteins were noted, such as using a "suppression of telomeric silencing protocol" using human nucleic acids expressed in yeast (page 36). The publication did not identify a human telomerase-associated protein having telomerase catalytic activity. Moreover, the nucleic acid and amino acid sequences described in the WO 96/12811 publication are not those of the TRT proteins or genes.

E. WO 96/40868 ("Essential Oligonucleotides of Vertebrate Telomerase," Cold Spring Harbor Lab/Greider et al., published in 1996) [FB] and Autexier et al., (1996, "Reconstitution of human telomerase activity and identification of a minimal functional region of the human telomerase RNA" *EMBO J.* 15:5928-35). [FI]

These publications described the use of partially purified telomerase extracts from human 293 cells in reconstitution experiments. The extracts were treated with micrococcal nuclease to destroy the telomerase RNA component (hTR) prior to reconstitution. The publications stated that telomerase activity, as assessed using an *in vitro* assay, could be restored by addition of the RNA component of human telomerase (hTR) or truncated variants. The publications also described the use of the "reconstituted" telomerase to screen for telomerase inhibitors.

No characterization of the protein subunits of human telomerase was provided in the publications. The publications described a cell extract partly enriched for telomerase activity, but did not identify the telomerase catalytic subunit or provide amino acid or nucleotide sequence for the hTRT protein or gene.

F. WO 96/19580 ("Telomerase Protein Component," Cold Spring Harbor Laboratory/Greider et al., published in 1996) [FC] and Related References. [DR, FG, FP]

The WO 96/19580 publication described the genes encoding two polypeptides purported to be subunits of *Tetrahymena thermophila* telomerase. The disclosed polypeptides were identified on the basis of copurification with *Tetrahymena* telomerase activity and were described as 80 kD and 95 kD polypeptides. WO 96/19580 also provided amino acid sequences and "synthetic genes" for the disclosed proteins. Methods for attempting to clone the human and mouse homologs of the 80 kD and 95 kD components were described in prophetic terms (page 32-36). These *Tetrahymena* proteins, along with the sequences of genes encoding them, were also described by Collins *et al.*, 1995, *Purification of Tetrahymena telomerase and cloning of genes encoding the two protein components of the enzyme*, *Cell*, 81: 677 [DR]. A rat homolog of the *Tetrahymena* p80 protein was described by Nakayama *et al.*, 1997, *TLP1: A Gene Encoding a Protein Component of Mammalian Telomerase Is a Novel Member of WD Repeats Family*, *Cell* 88:875-84 [FG]. A human homolog of the *Tetrahymena* 80 kD polypeptide described by Collins *et al.* is described by Harrington *et al.*, 1997, *A Mammalian Telomerase-Associated Protein*, *Science* 275:973-977 [FP].

The 80 kD and 95 kD proteins described in WO 96/19580 and other references were not disclosed as having telomerase catalytic activity. In addition, based on sequence comparisons, the 80 kD and 95 kD proteins are not homologs of the human or nonhuman (e.g., *Tetrahymena*) TRT polypeptides.

G. Lendvay *et al.*, 1996, "Senescence mutants of *Saccharomyces cerevisiae* with a defect in telomere replication identify three additional EST genes," *Genetics* 144:1399-1412. [DS]

Lendvay *et al.* described four yeast genes, *EST1*, *EST2*, *EST3*, and *EST4*, that play a role in telomere maintenance in *Saccharomyces cerevisiae*. Epistasis analysis demonstrated that the four EST genes function in the same pathway as the previously identified *TLC1* (which encodes the RNA subunit of *S. cerevisiae* telomerase).

The yeast *EST2* gene is identified in the Present Application and priority applications to be a *Saccharomyces cerevisiae* homolog of the human TRT. Lendvay *et al.*

differs from the present disclosure, in part, in that there was no teaching that the yeast *EST2* gene encoded a protein with catalytic activity. Lendvay et al. stated that the yeast *EST2* protein contained "no motifs that provide clues as to function" (abstract). In addition, Lendvay et al. did not describe or suggest the use of the yeast *EST2* gene sequence in any diagnostic or therapeutic methods, or describe or suggest the use of the yeast *EST2* polynucleotide for reconstitution of telomerase activity *in vivo* or *in vitro*.

H. GenBank Accession No. AA281296 [FJ]

This electronic GenBank listing provided an approximately 385 nucleotide sequence of a expressed sequence tag (EST) from a human germinal B-cell library. As disclosed in ancestor application USSN 08/844,419, the AA281296 EST was identified by a coinventor as corresponding to a conserved sequence in the TRT protein of the ciliate *Euplotes*. At the time of this identification, the coinventor was not subject to an obligation of assignment to both of the assignees of the Present Application.

The GenBank listing differs from the Present Application because, *inter alia*, it did not indicate or suggest the function of the EST sequence, or suggest that the AA281296 EST corresponds to a TRT sequence, or identify any protein coding sequence (e.g., open reading frame) in the EST sequence. In contrast, the Present Application discloses methods and reagents relating to hTRT gene and protein sequences.

The following references were co-authored by one or more of the inventors named on the Present Application, and published after one or more of the ancestor applications to which the Present Application claims priority, but prior to the filing date of the Present Application:

I. Lingner et al., 1996, "Purification of telomerase from *Euplotes aediculatus*: requirement of a primer 3' overhang" *Proc. Natl. Acad. Sci. USA* 93:10712 [FK]

This reference described the purification of telomerase from the ciliate *Euplotes aediculatus*, and identified two putative protein subunits of telomerase, one of approximately 43 kDa and one of approximately 120 kDa. The patent applications to which the Present

Application claims priority identify the 120 kDa protein as the *Euplotes* TRT protein and also describe the 43 kDa protein.

J. Lingner et al., 1997, "Reverse transcriptase motifs in the catalytic subunit of telomerase," *Science* 276: 561. [EA]

This reference described the cloning of the gene encoding the catalytic protein subunit of *Euplotes aediculatus* telomerase (*Euplotes* TRT, referred to as "p123" in this publication) and the identification of reverse transcriptase motifs in the *Euplotes* protein. Lingner et al. also identified EST2, a protein from *Saccharomyces cerevisiae*, as a homolog of the *Euplotes* TRT. The authors also showed that mutation in the reverse transcriptase motifs of the yeast TRT resulted in loss of telomerase activity *in vitro* and loss of function *in vivo*.

The following references were published after the filing date of the Present Application. They are included in order to assist the Examiner in understanding the invention.

K. Nakamura et al., 1997, "Telomerase Catalytic Subunit Homologs from Fission Yeast and Human," *Science* 277: 955. [FL]

This reference described the TRT genes and proteins from human and *Schizosaccharomyces pombe*. GenBank accession numbers for the *S. pombe* and *human* TRT sequences were provided (see legend to Figure 2). Several of the inventors named on the Present Application are coauthors of this article.

L. Counter et al., 1997, "The catalytic subunit of yeast telomerase." *Proc. Nat'l Acad. Sci. U S A.* 94:9202-9207. [FM]

Counter et al. identified the *S. cerevisiae* EST2 gene product as a subunit of yeast telomerase required for enzyme catalysis. One or more of the inventors named on the Present Application were provided with a preprint of this article prior to the filing date of U.S. Patent Application Serial No. 08/912,951 (filed August 14, 1997).

M. Meyerson et al., 1997, "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization," *Cell* 90:785-795 [FN]

Meyerson et al. described cloning of a human cDNA, "hEST2," that encodes the catalytic subunit of human telomerase. One or more of the inventors named on the Present Application were provided with a preprint of this article prior to the filing date of U.S. Patent Application Serial No. 08/912,951 (filed August 14, 1997), but after the filing date of U.S. Patent Application Serial No. 08/854,050 (filed May 9, 1997).

N. Kilian et al., 1997, "Isolation of a candidate human telomerase catalytic subunit gene, which reveals complex splicing patterns in different cell types," *Hum. Mol. Genet.* 6:2011-2019. [FO]

Kilian et al. describe cloning of a human gene, "hTCS1," that encodes a telomerase component. The authors identify the hTCS1 as the same gene as hTRT, citing Nakamura et al., *supra*.

O. Harrington et al., 1997, "Human telomerase contains evolutionarily conserved catalytic and structural subunits," *Genes Dev.* 11:3109-3115. [FP]

Harrington et al. described cloning and characterization of a human gene encoding "TP2" (telomerase-associated protein 2) which they reported is associated specifically with human telomerase activity. The authors identified TP2 as encoding the catalytic subunit of human telomerase referred to in the Present Application as hTRT, citing Nakamura et al. (reference K, *supra*).

P. Weinrich et al., 1997, "Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT," *Nat. Genet.* 1997 Dec 1; 17(4): 498-502. [FQ]

In this article, co-authored by three of the inventors named on the Present Application, Weinrich et al. described reconstitution of telomerase catalytic activity by *in vitro* co-synthesis (*i.e.*, a coupled transcription/translation system) of hTRT and the human telomerase RNA component. Reconstitution by *in vitro* mixing of hTRT and telomerase RNA is also described. In addition, Weinrich et al. reported that, as disclosed in the Present Application, single amino-acid changes in conserved telomerase-specific and "RT" motifs reduce or abolish activity telomerase catalytic activity.

Q. Bodnar et al., 1998, "Extension of Life-Span by Introduction of Telomerase into Normal Human Cells," *Science* 279:349-352. [FR]

In this article, co-authored by two of the inventors named on the Present Application, Bodnar et al. described the effect of expression of hTRT protein on the life-span of normal human cells. As disclosed in the Present Application, expressing hTRT in normal human cells results in an increase in the life-span of the cells.

R. WO 98/01543 ("Human Telomerase Gene" Tularik Inc., published in 1998) [FE] and WO 98/01542 ("Human Telomerase" Regents of the University of California, published in 1998). [FD]

These PCT publications were published after the filing date of the Present Application but claim priority to U.S. Patent Applications filed before the filing date of the Present Application. These publications described four protein bands identified by polyacrylamide gel electrophoresis of a cell lysate fraction "enriched for telomerase." The apparent molecular weights of the proteins on denaturing PAGE were: 140 kD, 105 kD, 48 kD and 43 kD. Amino acid and nucleotide sequences for the 105 kD protein and a corresponding cDNA were provided. Based on comparison of the sequences, the 105 kD protein does not appear to be related to the hTRT protein disclosed in the Present Application.

The following patent applications are related to the Present Application, either because they claim priority to the Present Application or because the Present Application claims priority to them. The brief descriptions given are not intended to be comprehensive or limiting.

1) USSN 08/724,643 (filed October 1, 1996), described, *inter alia*, isolated, purified, and recombinant telomerase reverse transcriptase (TRT) proteins, and isolated, purified, and recombinant nucleic acids relating to the TRT genes of the ciliate *Euplotes aediculatus* and the yeast *S. cerevisiae*. The inventors listed on this application are Cech and Lingner, and the application is assigned to the University Technology Corporation. It is the undersigned's belief that at the time any invention in this application was made, inventor Cech was subject to an obligation of assignment to the Howard Hughes Medical Institute, and inventor Lingner may or may not have been subject to a similar obligation, but Cech and Lingner are believed to be coinventors of each claim. Prior to the filing of USSN 08/844,419, the application was assigned to the University Technology Corporation.

2) USSN 08/844,419 (filed April 18, 1997), described, *inter alia*, the cloning of a *S. pombe* (yeast) homolog of the *Euplotes* TRT protein, and the identification of a human DNA expressed sequence tag (EST) in a public database that corresponded to a sequence in the *Euplotes* TRT. The inventors listed on this application are Cech, Lingner, and Nakamura, and the application is assigned to University Technology Corporation. It is the undersigned's belief that at the time of making of any invention which is in this application and not in USSN 08/724,643, inventors Cech, Lingner and Nakamura were subject to an obligation of assignment to the University Technology Corporation.

3) USSN 08/846,017 (filed April 25, 1997), provided, *inter alia*, additional hTRT amino acid and nucleotide sequence. The inventors listed on this application are Cech, Lingner, Nakamura, Morin, Harley, Andrews, and Chapman, and the application is assigned to University Technology Corporation and Geron Corp. At the time of invention of the invention(s) for which Morin, Harley, Andrews, and Chapman were coinventors, they were subject to an obligation of

assignment to Geron Corp, and inventors Cech, Lingner and Nakamura remained subject to an obligation of assignment to the University Technology Corporation.

4) USSN 08/851,843 (filed May 6, 1997) and USSN 08/054,050 (filed May 9, 1997), described, *inter alia*, isolation of a clone encoding a full-length hTERT protein, and provided amino acid and nucleotide sequence for hTERT. The inventors and assignees are the same as in USSN 08/846,017.

5) The following patent applications describe, *inter alia*, additional isolated, purified, and recombinant variants and fragments of the human and/or non-human telomerase reverse transcriptase peptides, polypeptides, proteins, oligonucleotides and polynucleotides, and methods for using these novel reagents:

USSN 08/911,312, filed August 14, 1997;

USSN 08/912,951, filed August 14, 1997;

USSN 08/915,503, filed August 14, 1997;

USSN 08/974,549, filed November 19, 1997;

USSN 08/974,584, filed November 19, 1997;

PCT Application US97/17618, filed October 1, 1997; and,

PCT Application US97/974549, filed October 1, 1997 (In addition, 6 national or regional applications were filed on October 1, 1997, with essentially the same disclosure as PCT Application US97/974549).

The inventors and assignees of these applications are the same as in USSN 08/846,017.

6) USSN 08/979,742 (filed December 29, 1997), disclosed, *inter alia*, isolated, purified, and recombinant preparations of the mouse homolog of hTERT, related polynucleotides, and methods relating to mouse TRT peptide, polypeptide, protein, oligonucleotide and polynucleotide reagents. The listed inventors are Morin, Allsopp, and DePinho, and the assignees are Geron Corp. and Albert Einstein College of Medicine.

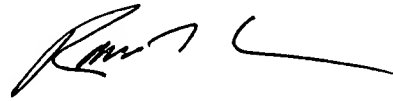
Summary

Applicants respectfully submit that the pending claims are presently allowable. No prior art references anticipated the claimed human telomerase catalytic subunit proteins, polynucleotides, and methods of the of the present invention, and no prior art references, either alone or in combination, rendered these proteins, polynucleotides or methods obvious.

Respectfully submitted,



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